ABSTRACT

*Corresponding Author
Yadav M. Bayakewar
Department of Pharmaceutics, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Behind Railway Station, New Kamptee, Dist. Nagpur-441002 (Maharashtra) India.

*Xanthium Strumarium* L. (Family: Asteraceae/ Compositae) a medicinal plant commonly found as a weed, folklore medicine and is found to be an ancient Ayurvedic remedy. It is an annual plant species belonging to the Asteraceae/ Compositae family. It is widely distributed in North America, Brazil, China, Malaysia and hotter parts of India. The herb is traditionally used mostly in treating several ailments. Extracts of the whole plant, especially leaves, roots, fruits and seeds have been applied in traditional medicine for the treatment of leucoderma, poisonous bites of insects, epilepsy, salivation, long-standing cases of malaria, rheumatism, tuberculosis, allergic rhinitis, sinitis, urticaria, rheumatoid arthritis, constipation, diarrhoea, leprosy, lumbago, pruritis, bacterial and fungal infections. This comprehensive account provides a botanical description of the plant, its Phytochemical constituents and pharmacological activities are reviewed, focussing on antibacterial, antitumor, antitussive, antifungal, anti-inflammatory, antinociceptive, hypoglycaemic, antimitotic, antioxidant, antitrypanosomal, CNS depressant activity, diuretic effects, contact dermatitis, insecticidal and herbicidal activities. Most of the pharmacological effects can be explained by the constituents like sesquiterpene lactones, glycoside, phenols, polyesterols present in all plant parts. However, future efforts should concentrate more on in vitro and in vivo studies and also on clinical trials in order to confirm traditional wisdom in the light of a rational phytotherapy. Because of its multi-activity, in particular, anti-tumour, anti-cancer activity, so much attention is focussed on the herb. Finally, research needs quantitation of individual constituents and assessment of their pharmacological activities in humans.
KEY WORDS: Xanthium Strumarium; pharmacological activities; phenols; phytotherapy; sulphated glycoside; Carboxyatractyloside.

INTRODUCTION

Xanthium strumarium (rough cocklebur, clotbur, common cocklebur, large cocklebur, woolgarie bur) is a species of annual plants belonging to the Asteraceae family. It probably originates in North America and has been extensively naturalized elsewhere. It is a commonly found as a weed in roadsides, rice fields, hedges throughout the tropical parts of India. The word “xanthium” is derived from an ancient greek word “xanthos” meaning yellow and “strumarium” means “cushion like swelling,” with reference to the seedpods which turn from green to yellow as they ripen (later they become deep yellow to brown). It is commonly called chota gokhru due to the shape of its fruit which look likes the cow’s toe. In many parts of India, it is known as adhasisi, as this weed is used for the treatment of common disease hemicrania."[1] The genus xanthium includes 25 species, all of American origin. Xanthium spinosum Linn and X. strumarium Linn are used medicinally in Europe, North America and Brazil; Xanthium canadens mill. is used in North America and Brazil and X. strumarium Linn. in china, India and Malaysia with the capability of causing acute liver failure in pigs, cattle, sheep, poultry and occasionally horses.[1, 2]

The plant produces allergic contact dermatitis in susceptible humans. Cocklebur was cultivated as a leafy vegetable in China. Young floral tops and the two leaves below are boiled in water and eaten as a pot-herb in Assam. The herb as such is suspected to be poisonous but the toxic substances are removed by washing and cooking.[2, 3] A highly toxic glycoside, Carboxyatractyloside, is present in the seeds and seedlings of cocklebur. The amount of the chemical was measured to be 0.457% in the seeds and 0.12% in the seedling at the two-leaf stage. The poison occurs only in the cotyledons or seed leaves of the seedlings. The toxin readily disappears after germination.[1]

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X. strumarium leaves have reported to contain alkaloids, flavonoids (flavonol), anthraquinone, cardenolide, leucoanthocyanin, simple phenolics (Catechol) and triterpenoids. Several studies have reported X. Strumarium include phenolic compounds as thiazolidinediones, chlorogenic acids, ferulic acids, 1,3,5-tri-0-caffeoyl quinic acid, 1,5-di-caffeoyl quinic acid, caffeic acid, as well as isoprenoids such as stigmasterol, β-sitosterol, monoterpane and sesquiterpene hydrocarbons, triterpenoids saponins.\cite{1,4,5,6,7}

**GEOGRAPHY AND SEASONALITY**

The most common cocklebur, X. strumarium, is found throughout North America. Poisoning in animals occurs most often in the spring and summer when growing conditions favor germination of the seedlings. The mature plants are prolific bur producers; consequently, massive numbers of seedlings may germinate at once, increasing the potential for poisoning to occur. Cockleburs are annual erect, branching plants up to 6 feet in height with a taproot. The leaves are large and simple and alternate with serrated edges. Flowers are produced in leaf axils or terminally on branches. Characteristic burs turn brown when mature.\cite{1,6,7} X. strumarium is an annual herb, up to 1 m in height, with a short, stout, hairy stem and commonly grows in waste places, roadsides and along river banks in warmer parts. Leaves broadly alternate are triangular-ovate or sub orbicular, light and bright green in colour in an alternate pattern with irregular lobes and relatively inconspicuous teeth, 5–15 cm long, often three-lobed, with prominent veins, long petiole, scabrous on both sides. Stems are round or slightly ribbed, often speckled with purple and have short white hairs scattered across the surface; flower heads are in terminal and auxiliary racemes, and are white or green; numerous male uppermost, female ovoid, covered with hooked bristles.\cite{1}

Fruits are obovoid, enclosed in the hardened involucres, with two hooked beaks and hooked bristles. Flowering time in India is August-September. This weed is easily dispersed through animals as the fruits have hooked bristles and two strong hooked beaks. It flowers from July to October, and the seeds ripen from August to October.
The flowers are monoecious and are pollinated by insects. The plant is self-fertile.\textsuperscript{[1, 2, 5]} The fruits are harvested when ripe and dried for use. The plant may have some medicinal properties and has been used in traditional medicine in South Asia and traditional Chinese medicine. In Telugu, this plant is called Marula Matangi. However, while small quantities of parts of the mature plants may be consumed, the seeds and seedlings should not be eaten in large quantities because they contain significant concentrations of the extremely toxic chemical Carboxyatractyloside.\textsuperscript{[2, 3, 4]} The mature plant also contains at least four other toxins. Animals have also been known to die after eating the plants. A patient consuming a traditional Chinese medicine containing cocklebur called \textit{Cang Er Zi Wan} developed muscle spasms. It was responsible for at least 19 deaths and 76 illnesses in Sylhet District, Bangladesh, 2007. People ate large amounts of the plants, locally called \textit{ghagra shak}, because they were starving during a monsoon flood and no other plants were available. The symptoms included vomiting and altered mental states, followed by unconsciousness.
PHYTOPHARMACOLOGICAL ACTIVITY

The whole plant, especially root and fruit, is used as medicine. According to Ayurveda, the plant has cooling, laxative, fattening, anthelmintic, alelteric, tonic, digestive, antipyretic activities and improves appetite, voice, complexion and memory. It cures leucoderma, biliousness, and poisonous bites of insects, epilepsy, salivation and fever. The plant has been reported as fatal to cattle and pigs. It is used by various Native American tribes to relieve constipation, diarrhea and vomiting.\[^1, 11, 44, 46\] Indigenous Chinese applications are as a headache remedy and to assist with cramping and numbness of the limbs, ulcers and sinus problems. The plant is considered to be useful in treating long-standing cases of malaria and is used as an adulterant for *Datura stramonium*.

The leaves and roots are used for their anodyne, antirheumatic, antisyphilitic, appetizer, diaphoretic, diuretic, emollient, laxative and sedative activities. An infusion of the plant has been used in the treatment of rheumatism, diseased kidneys and tuberculosis. It has also been used as a liniment on the armpits to reduce perspiration. The fruits contain a number of medically active compounds including glycosides and phytosterols.\[^1, 10\] They are anodyne, antibacterial, antifungal, antimalarial, antirheumatic, antispasmodic, antitussive, cytotoxic, hypoglycemic and stomachic. They are used internally in the treatment of allergic rhinitis, sinusitis, urticaria, catarrh, rheumatism, rheumatoid arthritis, constipation, diarrhea, lumbago, leprosy and pruritus. They are also used externally to treat pruritus and small pox. The ashes are applied to sores on the lips and mucous membrane of the mouth. The root is a bitter tonic and febrifuge. It has historically been used in the treatment of scrofulous tumors and used locally on ulcers, boils and abscesses. The paste of green spiny fruits is used against migraine and the juice of leaves and fruits are believed to be useful for smallpox and the roots are used for cancer.\[^1\]

The burs are used in china as a tonic, diuretic and sedative. A decoction of the root has been used in the treatment of high fevers, leucorrhoea and to help a woman expel the afterbirth. A decoction of the seeds has been used in the treatment of bladder complaints. A poultice of the powdered seed has been applied as a salve on open sores. Seeds yield semidrying edible oil (30–35%) which resembles sunflower oil and is used for treating bladder infections, herpes and erysipelas.\[^40, 42, 43\] The dried leaves are a source of tannin. A yellow dye is obtained from the leaves. The seed powder has been used as blue body paint. The dried plant repels weevils from stored wheat grain. The seed contains an essential oil.
Xanthium is defined as a toxic herb in Chinese Pharmacopoeia. Patients taking over 100 g of the fruit may complain of malaise, headache and gastrointestinal disturbance in 12 hours. Other toxic symptoms in humans include dizziness, drowsiness and coma, generalized tonic seizure, appearance of jaundice, hepatomegally, impairment of liver function, proteinuria, cylindruria, and haematuria.[1]

The toxic substance soluble in water is extensively used for the treatment of sinus congestion. Its modern uses are mainly for allergy-type disorders, specifically allergic rhinitis, atopic dermatitis (urticaria), chronic paranasal sinusitis and chronic eczema.

PHYTOCHEMICALS

The aerial parts of the plant contain a mixture of unidentified alkaloids, which are said to be toxic. Besides alkaloids, the aerial parts of the plant contain sesquiterpene lactones, viz. xanthisinin; its stereoisomer, xanthumin, xanthatin (deacetyl-xanthisinin); a toxic principle, a sulphated glycoside: xanthostrumarin, atractyloside, carboxyatractyloside; phytosterols, xanthanol, isoxanthanol, xanthinosin, 4-oxo-bedfordia acid, hydroquinone; xanthanolide; caffeoylquinic acids; α and γ-tocopherol; thiazinedione, 4-oxo-1(5),2,11,(13)-xanthatriene-12,8-olide, known as “deacetyl xanthumin” an antifungal compound; linoleic acid. The main toxic compound isolated from the plant has been identified as carboxyatractyloside, a kaurene glycoside previously called xanthostrumarium. In addition to carboxyatractyloside CAT, potentially toxic ingredients include several sesquiterpene lactones (e.g. guaianolides, germacranolides, and elemanolides). Aerial parts contain three xanthanolide and xanthanetype sesquiterpenoids, 11α,13-dihydroxanthatin, 4β,5β-epoxyxanthatin-1α,4α-endoperoxide, 1β,4β,4α,5α–diepoxyxanth-11(13)-en-12-oic acid, a dimeric xanthanolide, sesquiterpene lactones, 8-epixanthatin, 2-epixanthumin and 8-epi-xanthatin-5β-epoxide.[1,8,14]

The phenols isolated are caffeic acid, potassium3-O-caffeoylquininate, 1-O-cafeoyl quinic acid, chlorogenic acid, 4-O-cafeoylquinic acid, 1,4-di-O-cafeoylquinic acid, 1,5-di-O-cafeoylquinic acid, 3,5-di-O-cafeoylquinicacid, 4,5-di-O-cafeoylquinic acid, 1,3,5-tri-O-cafeoylquinic acid, 3,4,5-tri-O-cafeoylquinic acid, and cynarin. The toxic principles of the seeds are hydroquinone, choline and a third more toxic unidentified compound. Besides these, the seeds also contain considerable amount of iodine. The fruits are rich in vitamin C. The powdered shell of fruit can be used for making activated carbon.[1] The shells contain 15.9% pentosans and can be used as a raw material for the synthesis of furfural. The young fruit contains glucose, fructose, sucrose, organic acids, phosphatides, potassium nitrate, β-
sitosterol, γ-sitosterol, β-d-glycoside of β-sitosterol called strumaroside. The total free amino acid content is 1.65%. It includes amino-n-butyric acid, arginine, aspartic acid, cystine, glutamic acid, methionine, proline, tryptophan in micromoles per milligram dry weight.

The oil is light yellow, odorless and has the same taste as other vegetable oils. Oil contains d-limonene (35.0%), d-carveol (25.0%), α-ionone (10.5%), terpinolene (7.0%), β-caryophyllene (6.0%) and p-cymene (5.0%).[40, 42, 43] The essential oil obtained by hydrodistillation of the stems and leaves was analyzed by gas chromatography (GC) and GC/mass spectrometry (MS). Twenty-two compounds representing 86.4% of the stem oil were identified, among which bornyl acetate (19.5%), limonene (15.0%) and β-selinene (10.1%) were the major ones.[1]

PHARMACOLOGY OF X. STRUMARIUM
It is found as a noxious weed in maize fields, along roadsides, wastelands and around cattle kraals. It is known to occur on the sandy river beds in the Matebeland province where it would be accessible to extensively reared pigs and cattle and causes intoxication of these animals. The toxicity of this plant is largely unknown in this country; it has not been implicated for causing livestock losses.[1] The herb has several health-promoting benefits, including antibacterial, antitumor, anticancer, antifungal, anti-inflammatory, antinociceptive, antitussive, hypoglycemic, antimitotic, antitypanosomal, antimalarial, diuretic, antioxidant, analgesic, repellent and insecticidal activities.[6, 7]

Antibacterial, Antitumor and Anticancer Activities
The xanthinin contained in plant acts as a plant growth regulator and has antibacterial activity. Seed yields semi-dry edible oil (30–35%) which resembles sunflower oil and is used in bladder infection, herpes, and erysipelas. Two xanthanolide sesquiterpene lactones, 8-epi-xanthatin and 8-epi-xanthatin-5β-epoxide, isolated from the leaves demonstrated significant inhibition on the proliferation of cultured human tumor cells, the plant extract exhibited antimicrobial activity against Proteus vulgaris, Staphylococcus aureus, Bacillus subtilis, Candida albicans and Candida pseudotropicalis. The activity is due to presence of xanthol.[1, 2, 11]

Disc-diffusion assay
Antimicrobial tests were carried out by the disc diffusion method using 100 μL of bacteria suspension (containing $2.0 \times 10^8$ CFU/mL of bacteria) dispersed on MHA in sterilized Petri
dishes (60 mm in diameter). To the discs (6 mm in diameter, HI Media Laboratories Pvt. Ltd., Mumbai, India) placed on the inoculated agar, 50, 100, 200, and 300 μL of leaf extracts were added. The inoculated plates were maintained at 4°C for 2 h and later incubated at 37°C for 24 h. Antimicrobial activity was determined by measuring the zone of inhibition (mm) against the test bacterial (methicillin-resistant S. aureus (MRSA) and methicillin-sensitive S. aureus (MSSA) strains.

**Antifungal Activity**
The plant has potent antifungal activity against pathogenic as well as non-pathogenic fungi due to the presence of terpenes, d-limonene and d-carveol. The leaf extract of plant may be used as a potent fungi toxicant against the mycelial growth of *Fusarium moniliforme*. Hexane extract showed marked inhibition against *C. albicans, Aspergillus Niger, P. aeruginosa* and *S. aureus* at a concentration of 200μg/disc. Ethyl acetate extract showed an inhibition against *A. niger, S. aureus* and *E. coli* at a concentration of 200μg/disc. Alcoholic extract showed an inhibition only against *S. aureus* at a concentration of 200μg/disc. The plant possesses significant potency against *C. neoformans* and *Candida* species with low toxicity to brine shrimps.[1]

**Hypoglycemic Activity**
Cockleburs as such provide a relatively inexpensive source of raw material for worldwide production of a naturally occurring insulin substitute. The main advantage is that the product does not produce its results by causing production of insulin by stimulation of Islets of Lagerhans in the pancreas. The plant exhibited potent hypoglycemic activity in the rat. The antihyperglycemic effect of caffeic acid and phenolic compounds present in the fruit of *X. Strumarium* was investigated. After an intravenous injection of caffeic acid into diabetic rats of both streptozotocin-induced and insulin-resistant models, a dose-dependent decrease of plasma glucose was observed. However, a similar effect was not produced in normal rats. An insulin independent action of caffeic acid can thus be considered. Otherwise, this compound reduced the elevation of plasma glucose level in insulin-resistant rats receiving a glucose challenge test. Also, glucose uptake into the isolated adipocytes was raised by caffeic acid in a concentration-dependent manner. Increase of glucose utilization by caffeic acid seems to be responsible for the lowering of plasma glucose. Carboxyatractyloside also possesses hypoglycemic activity.[1]
Antimitotic Activity

*X. strumarium* may possess antimitotic components. In a study, the plant was screened for its antimitotic activity using the microtubule-tubulin system isolated from mammalian tissue. The separated fractions obtained were identified and used for *in vitro* polymerization studies. The whole as well as partially separated chemical constituents showed effective inhibition of tubulin polymerization.¹

Contact Dermatitis

The plant is suspected to cause air-borne contact dermatitis. In a study, patch tests with a 15% aqueous extract of air dried leaves showed a severe positive reaction. The titre of contact hypersensitivity with the plant extract was more than 1:100,000 and for *Parthenium hysterophorus* it was 1:10, indicating a high degree of hypersensitivity to *X. strumarium*. Further tests in 14 other patients revealed a high prevalence of cross sensitivity between the two plants. The antigens in the two plants seem to be very similar.¹,¹³,¹⁴,¹⁵

Antioxidant Activities

Antioxidant activity was determined by the paired diene method. The antioxidant activity measured represents the capacity of the plant extract to inhibit the peroxidation of linoleic acid, in which the double bond is changed to a paired diene. Each extract sample (0.01-30 mg/mL) in methanol (100μl) was blended with 3 mL of 10mM linoleic acid (Sigma Chemical Co., St. Louis, MO, USA) to form an emulsion in 0.2 M sodium phosphate buffer (pH 6.6) in test tubes, and then placed in the dark at 37°C to stimulate oxidation. After incubation for 17 h, 7 mL of 70% methanol in deionized water was added, and the absorbance of the mixture was measured at 234 nm against a blank in a Hitachi U-2001 spectrophotometer (Tokyo, Japan). Antioxidant activity was measured as follows:

\[
\text{Antioxidant activity (\%) = } \left[ \frac{(\Delta A_{234} \text{ of control} - \Delta A_{234} \text{ of sample})}{\Delta A_{234} \text{ of control}} \right] \times 100.
\]

IC₅₀ value (mg/mL) is the efficient concentration at which the antioxidant capacity was inhibited by 50%, and was gained by interpolation from linear regression analysis. Analyses were repeated 3 times (technical replicates). α-tocopherol, butylated hydroxyanisole (BHA) and ascorbic acid (Sigma-Aldrich, USA) were used as standard controls.¹,²

Diuretic Activity

The method of Lipschitz et al.¹⁰ was employed for the assessment of diuretic activity. Albino rats of either sex deprived of food and water 18 h prior to the experiment were divided into four groups. Group-I received only normal saline and served as control. Group-II
received furosemide at a dose of 5 mg/Kg, p. o. and it was considered as positive control group. Group-III and Group-IV received the PEE, at doses of 250 and 500mg/Kg, p.o. respectively. After oral administration, each animal were placed in an individual metabolic cages specially designed to separate feces and urine at room temperature. The observed parameters were total urine volume for 5 hours, Na\(^+\) and K\(^+\) excreted in urine. The concentration of electrolytes in urine is expressed in terms of mmol/L and the urine volume is expressed in mL/100g/5 h. Na\(^+\) and K\(^+\) concentrations were measured by flame photometer and Cl concentration was estimated by titration with silver nitrate solution (N/50) using three drops of 5% potassium chromate as an indicator.\(^{[11]}\) The results obtained were compared with the control and analyzed by student’s- T test.\(^{[1,16]}\)

**Neuropharmacological Activity**

Earlier study reported that *X. Strumarium* has significant anti-inflammatory and analgesic properties in mice. The whole plant used to treat cytotoxicity and antitumor activity. Furthermore, several investigations have reported that *X. strumarium* possesses anti-ulcerogenic, anthelmintic, diuretic, antimicrobial, antioxidant, and antilipidemic activity. *X. strumarium* traditionally used central nervous system (CNS) stimulant agent which may have potential antidepressant activity. Our current study designed to confirm the anti-depressant effects of *X. strumarium* mice model.\(^{[1]}\)

**Anti-depressant activity test**

*Tail suspension test:* The tail suspension test (TST) conducted as initially described by Steru et al. (1985) with modifications.\(^{[17]}\) One hour after oral administration and 30min after intraperitoneal injection of test compounds, mice individually suspended by the tail from a horizontal ring-stand bar raised 30 cm above the floor using adhesive tape placed 1 cm from the tip of tail and positioned such that the base of their tail was aligned with the horizontal plane. Test sessions lasted for 6min. Behaviors for the last 4 of the 6min period were then analyzed. Immobility was measured, a mouse judged to be immobile when it hung by its tail without engaging in any active behavior.

Xanthumin showed CNS depressant activity. Rodents treated with the plant extract exhibited alterations in general behavior patterns, reduction in spontaneous motility, prolongation of pentobarbitone-induced sleep, suppression of exploratory behavior patterns, and avoidance response.\(^{[1,3]}\)
Repellent and Insecticidal Effects

The repellent effects of the extracts of *X. strumarium* fruits and leaves diluted with 1/6, 1/8, 1/10 water (w/v) for fruits and 1/6, 1/8 (w/v) for leaves were investigated with randomized plot design and 25 replicates under laboratory conditions. It was found that the insecticidal effect was low, whereas the repellent effect was quite high. On the other hand, the effect of 1/6 concentration of fruit extract against adult and larvae of Colorado potato beetle was investigated under field conditions and the repellent effect was confirmed. This effect may appear because of toxic components of the fruits and leaves of *X. strumarium*. Low toxic components were hydroquinone and xanthatin. These components are known as repellent components.

In laboratory experiment, it was found out that repellent effect was high, insecticidal effect was low. The experiment related with the repellent effect, fruit concentrations inhibited the feeding of adult and four larvae stages. In the experiment of leaf concentrations, adult and larvae fed with treated leaves in some extent. As larval stage progressed feeding has increased. The concentration of fruit extract has significantly inhibited feeding. Low insecticidal effect was determined. This effect may appear because of toxic components of the fruits and leaves of *X. strumarium*. Low toxic components were hydroquinone and xanthatin. These components are known as repellent components. The effect of 1/6 fruit concentration decreased from 100% to 59.91% in 1993 and to 67.69% in 1995 in twenty first days in field experiment. The reason of decrease was that the females were laid their eggs on treated plants from seventy day to twenty first days. The number of larvae increased but they did not feed on the treated plants. Damage rates were very low on treated plants. \[17, 18\]

Antiallergic Activity

The aqueous extract of dried fruit of *X. strumarium* exerts inhibitory dose-dependent effect on mast cell mediated allergic reaction. The extract inhibited local immunoglobulin E (IgE) mediated passive cutaneous anaphylactic reaction. When 0.1 mg/ml *Xanthii fructus* was added, the secretion of TNF-α from anti-dinitrophenyl (DNP) IgE antibody stimulated mast cells were inhibited by 56%. Hence, fruits of the plant may be beneficial in the treatment of various types of allergic or inflammatory diseases.

The fruits of Xanthium strumarium L. (Asteraceae) have been used extensively in China for treatment of various diseases such as allergic rhinitis (AR), tympanitis, urticaria and arthritis or ozena. This study was designed to systemically investigate the effects of the
caffeoylxanthiazonoside (CXT) isolated from fruits of X. strumarium on AR in rodent animals. Animals were orally administered with CXT. Anti-allergic activity of CXT was evaluated by passive cutaneous anaphylaxis test (PCA); acetic acid-induced writhing tests were used to evaluate the analgesic effects of CXT; acetic acid-induced vascular permeability tests were performed to evaluate anti-inflammatory effect of CXT. Then, the model AR in rats was established to evaluate the effects of CXT on AR with the following tests: the sneezing and nasal scratching frequencies, IgE level in serum, and histopathological examinations. Our results demonstrated that CXT had favorable anti-allergic, anti-inflammatory and analgesic effects. Additionally, we found that CXT was helpful to ameliorate the nasal symptoms and to down-regulate IgE levels in AR rats. Thus, we suggested that CXT can be treated as a candidate for treating AR.[1, 6, 19, 20]

Anti-arthritic activity
Xanthium strumarium L. fruit (Xanthiu fruit) has been traditionally used as a medicinal herb in China for the treatment of many ailments including rheumatoid arthritis. When it was experimentally studied by Lin et al (2014), it significantly suppressed paw swelling and arthritic score increased body weight loss and decreased the thymus index The overproduction of (tumor necrosis factor) TNF-α and IL-1β was remarkably suppressed in the serum of all ethanolic xanthium strumarium (EXS)-treated rats, and in contrast, IL-10 was markedly increased. The level of COX-2 and 5-LOX was also decreased with EXS treatment.[1, 18]

Ten phenolic acid derivatives were identified from 14 detected peaks by HPLC-DAD with the reference substances and verified by LC–MS. These results suggest the potential effect of EXS as an antiarthritis agent towards (complete Freund’s adjuvant) CFA-induced arthritis in rats. Xanthium strumarium has the potential to be regarded as a candidate for use in general therapeutics and as an immune-modulatory medicine in rheumatoid arthritis.

Analgesic and anti-inflammatory effects
Hen et al (2007) demonstrated that the polar fraction of XSF has got most significant anti-inflammatory and analgesic properties in mice in a dose-dependent manner.[3] Bioassay-guided fractionation of ethanolic extract led to the isolation and identification of ten caffeoylquinic acids and three heterocyclics by HPLC–DAD–MSn from the active n-butanol fraction, implying that the active compounds are polar in nature. The isolated caffeoylquinic acids could partially explain the antinociceptive effect of X. strumarium polar extract.
Bader et al (2013) showed that the crude extract of X. spinosum roots from Jordanian origin dose dependently inhibited the 5-LOX (IC50≅10μg/mL), COX-1(IC50≅50μg/mL), and 12-LOX (IC50≅170μg/mL) enzymatic pathways in intact pro-inflammatory cells. A direct activity at the level of PLA2 was not probable, but the extract induced the synthesis of the anti-inflammatory eicosanoid 15(S) - HETE, which may, in turn, inhibit this enzyme.\cite{18}

**TOXICITY**

*X. strumarium* is poisonous to mammals. It is reported to have medium to strong allergenic effects. The toxic principle is a sulphated glycoside, Carboxyatractyloside, found in the seeds and during the two-leaf seedling stage. The mature plant is reported as non-toxic, although toxicosis has been reported in cattle which had ingested mature plants with burs despite the general belief that ingestion of burs should be limited by mechanical injury during mastication. Carboxyatractyloside (CAT) is a plant growth inhibitor. It has been hypothesized that it functions in a germinating seed to keep the second seed in the fruit capsule dormant so that its development is delayed until the next year. Cocklebur fruits, the portion used in Chinese herbal medicine, have the risk of high Carboxyatractyloside content, particularly in the spines. CAT is water soluble but is not destroyed by boiling (decocting) and probably not washed away by simple rinsing.\cite{1}

Rather, removing the prickles appears to be the best way to reduce the toxic component, which is partly accomplished by stir-frying alone. When ingested in sufficient quantities by animals, it produces hypoglycemia and hepatic damage; the latter possibly is due to increased vascular permeability in response to severe hypoglycemia. The mechanism of action has been proposed to be an uncoupling (disruption) of oxidative phosphorylation, a process essential for cell's energy metabolism and transfer system. In addition to CAT, it contains potential toxic ingredients like several sesquiterpene lactones that can cause vomiting, weakness, tremors, weak pulse, loss of appetite and convulsions in high doses. Marked hypoglycemia, elevated serum glutamate oxaloacetates transaminase and serum isocitric dehydrogenase concentrations occurred in pigs with acute hepatic necrosis, which had received cocklebur seedlings, ground bur or Carboxyatractyloside xanthatin.

**CASE REPORT**

A 25-year-old woman was referred to our emergency department because of altered mental status and an episode of tonic colonic seizure. She had 4 days period of anxiety, depression and muscular twitching. She lived in a village with her husband and had no serious past
medical history. On admission, her vital signs were normal except tachycardia (102/min). She was responsive only to pain stimuli. Initial bedside rapid glucose concentration was 40 mg/dL, thus she received 50 gm IV D50W. Reevaluation revealed clear improvement in her level of consciousness. In first laboratory data, she had hypoglycemia, prolonged coagulation profiles, elevated liver and kidney enzymes. Abdominal sonography showed hepatomegally, diffuse hyper-echoic changes in liver and mild as cits, gall bladder was distended and edematous without any stone.

Axial Brain CT scan and EEG were unremarkable. After three hours of conservative treatment by IV Dextrose, she was completely conscious and could be able to answer the questions of interviewers. She told that she is very interested in having child and her medical follow up could not solve her childlessness problem, so she clung to herbal medicine and an herbal medicine expert had suggested drinking an herbal compound. It consisted of leaves, stalk and seeds of an unknown plant. She had to drink a cup of the prepared liquid after decocting in water once a day (each aliquot has a dry weight about 30-40 gm) and her symptoms began 3 days after that. Her husband brought the plant to our hospital. By searching about poisonous plants of Iran and their effects, it was shown that the plant has scientific name: "Xanthium Strumarium" (Figure 1). She was asymptomatic during hospital course. There was no microorganism growth in blood and urine culture. The patient discharged on 7th day of admission. Her liver enzymes became normal within 3 months. She never used the plant again. She is still living in a small village and adopted a beautiful boy as one's own child.

Its seedlings and seeds contain the glycoside Carboxyatractyloside and can be poisonous to animals, including cattle, horses and pigs. Carboxyatractyloside poisoning causes multiple organ dysfunctions and can be fatal. Coagulation abnormalities, hyponatraemia, marked hypoglycemia, hepatic and renal failures are signs of a poor prognosis. There is no antidote for it and supportive therapy is the mainstay of treatment (Martin et al., 1986). The plant also has been used for medicinal properties for Cancer (Turgut et al., 2005), tuberculosis, wounds, headache, malaria, rheumatism (Fouche et al., 2008) and antibacterial activity against Staphylococcus aureus species (Gautam et al., 2007). The mature plant is reported as non-toxic; although toxicity has been reported in cattle which had ingested mature plants with burs despite the general belief that ingestion of burs should be limited by mechanical injury during mastication.
There are a few case reports about Xanthium Strumarium poisoning in humans. Those patients presented with acute onset abdominal pain, nausea and vomiting, drowsiness, palpitations, sweating and dyspnea. Some of them developed convulsions followed by loss of consciousness and death (Yokoe et al., 2008). Also the allergenic components presented in whole pollen extract of Xanthium Strumarium causing contact dermatitis especially in atopic patients (Witie et al., 1990; Mondal et al., 1998; Menz and Winkelmann, 1987). Our case showed multi organ failure (raised liver enzymes, elevated BUN and creatinine levels and coagulopathy) and an episode of seizure (due to hypoglycemia) that were similar to previous cases (Jaggi and Gangal, 1987), but in literature review we didn’t find any case with anxiety, depressing mood and muscular twitching due to Xanthium Strumarium poisoning. Also reported cases had sudden onset of symptoms unlike our case that had gradual onset.[9]

CONCLUSION
From the above given data, it is reviewed that Pharmacological studies have generally confirmed the traditional use of extract of whole plant, root, leaves and fruits as an ailment for leucoderma, poisonous bites of insects, epilepsy, salivation, long-standing cases of malaria, rheumatism, tuberculosis, allergic rhinitis, sinitis, urticaria, rheumatoid arthritis, constipation, diarrhea, leprosy, lumbago, pruritis, and inflections due to bacteria and fungus. Most of the biological effects can be explained by the high amount of xanthatin, xanthanolide sesquiterpene lactones (antibacterial, anticancer, antitumor), desacetyl xanthumin (antifungal), xanthanol, xanthumin (CNS depressant), thiazinedione, desacetyl xanthumin (antifungal), Carboxyatractyloside, caffeic acid derivative (hypoglycemic) and its quinic acid derivatives (hypoglycemic, anti-inflammatory, analgesic) and terpenes (antioxidant) present in all plant parts.

The pharmacological studies so far have mostly been performed in vitro and in vivo with animals. Therefore, clinical studies are urgently needed in order to confirm traditional wisdom in the light of a rational phytotherapy. Even today, plants are the almost exclusive source of drugs for a majority of the world’s population. Therefore, it remains a challenge for scientists to provide efficient, safe and cheap medications, especially for rural areas. The plant is widely distributed in North America, Brazil, china, Malaysia and hotter parts of India. Their quantification of individual phytoconstituents as well as pharmacological profile based on in vitro, in vivo studies and on clinical trials should be further investigated.
REFERENCES
16. M.A Halkai
1, Arun Patil
1, MD Akhil Ahmed
1, AK Beknal
1: diuretic activity of fruit extract of xanthium strumarium l in albino rats.


19. Peng W
1, Ming QL
2, Han P
3, anti-allergic rhinitis effect of caffeoylxanthiazonoside isolated from fruits of xanthium strumarium l. in rodent animals, 2014 May 15; 21(6): 824-9.


55. https://www.google.com/search?q=xanthium+strumarium+flowers&sxsrf=ACYBGNQXI F3HnhQeqg828A85Lk9fDjoK3BA:1569388183249&source=lnms&tbn=isch&sa=X&ved =0ahUKEwia_bTJmuvkAhVbQN4KHb (Figures)

56. https://www.google.com/search?q=xanthium strumarium images